CASE/0303/09/24

EMPLOYEES v THERAMEX

Allegations regarding regulatory compliance and leadership accountability

CASE SUMMARY

This case was in relation to a complaint comprising concerns about the leadership, processes and compliance culture at Theramex, with specific allegations relating to prescribing information and clinical trials/non-interventional studies.

The outcome under the 2021 Code was:

Breach of Clause 2	**Bringing discredit upon, and reducing confidence in, the pharmaceutical industry**
Breach of Clause 4.7 (x2)	**Failing to publish the summary details and results of non-interventional studies of marketed medicines**
Breach of Clause 5.1 (x4)	**Failing to maintain high standards**
Breach of Clause 8.3 (x2)	**Failing to certify protocols relating to non-interventional studies**
Breach of Clause 12.1 (x4)	**Failing to provide accurate and up-to-date prescribing information**

No Breach of Clause 4.6 (x2)	**Requirement to disclose details of clinical trials**

The Panel reported the company to the Appeal Board in accordance with Paragraph 10.2 of the Constitution and Procedure for it to decide whether further sanctions were appropriate.

The Appeal Board considered the case in May 2025 and decided, in accordance with Paragraph 13.4 of the Constitution and Procedure, that a senior representative of Theramex should be invited to attend a future Appeal Board meeting to report on progress and confirm that appropriate action had been taken.

On 28 January 2026, Theramex advised the PMCPA that it would no longer accept the jurisdiction of the PMCPA and did not want to be part of the self-regulatory framework for the pharmaceutical industry in the UK. The PMCPA has informed the Medicines and Healthcare products Regulatory Agency (MHRA) of Theramex's decision.

Theramex decided not to attend the Appeal Board meeting on 26 February 2026 and declined the opportunity to make any further written submission in relation to this case.

The Appeal Board publicly reprimanded Theramex for its failings and the potential impact on patient safety. The Appeal Board also required an audit of Theramex's procedures in relation to the Code to be carried out by the PMCPA. Theramex must

comply with the requirement for a PMCPA audit, should it request to rejoin self-regulation in the future.

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A complaint about Theramex HQ UK Ltd was received from a named, contactable person who explained that they were writing on behalf of a group of concerned employees.

COMPLAINT

The complaint wording is reproduced below with some typographical errors corrected:

> "We are a group of employees from various cross-functional teams at Theramex, and we are writing to express our growing concerns regarding the company's adherence to regulatory standards and the accountability of its leadership. While we have attempted to escalate these issues internally on numerous occasions, there has been a consistent lack of action or meaningful response, which leaves us with no choice but to seek external guidance and support.
>
> We are particularly troubled by the lack of clear leadership from the Executive Leadership Team, specifically the [named senior medical role] and [named senior commercial role], whose guidance has been both absent and inconsistent.
>
> Despite repeatedly raising concerns about the lack of processes governing the updating of prescribing information, there has been no substantive action. For instance, some products, such as Intrarosa, have not had their prescribing information updated since 2019, leaving us concerned that important safety data may have been omitted from our portfolio of drugs due to a lack of interdepartmental accountability. This issue is of significant concern, especially as it affects countries reliant on prescribing information provided by our global offices in the UK. There have even been instances where senior leaders have publicly mentioned that Regulatory Affairs does not communicate changes to the Summary of Product Characteristics (SPCs).
>
> Despite receiving multiple complaints, both through the PMCPA and from other companies, we have not been provided with any details about the nature of these complaints. Without this information, we are unable to learn from past mistakes or implement corrective measures to prevent future complaints.
>
> We also wish to bring to your attention concerns regarding compliance with clinical trial requirements. Numerous trials, particularly real-world evidence studies presented at international congresses, do not meet Code standards. This includes failure to certify protocols, publish findings, or highlight the trials on appropriate websites.
>
> The lack of resources within Theramex's global headquarters to ensure compliance with these standards is alarming. We are being pressured by Senior Leadership to meet short deadlines, with compliance is being treated as an afterthought. In fact, it has

been suggested that, should compliance issues arise, we should blame the Signatory responsible for certifying the material. This blame culture is deeply concerning and detrimental to fostering a respectful and collaborative work environment.

In May, a meeting was organised and attended by senior leadership, attended by the [senior leader] to clarify roles and responsibilities, but no outputs or changes in behaviour have resulted from this meeting. We are also still awaiting the results of an internal audit on the approval/ certification process for promotional and non-promotional material, which has not been shared. We believe it is because the results will show a complete lack of understanding of the Code.

We are afraid that providing too many specific details might lead to retaliation from management, but we have lost faith in our internal escalation process. As such, we feel compelled to outline these concerns to the PMCPA.

Please feel free to contact us should you have any questions or require further information. We sincerely hope that with your intervention, these serious issues will be addressed to ensure both compliance and ethical leadership within the company."

The complainants provided the following further information following a request from the case preparation manager:

"Thank you for your continued attention to this matter. We would like to respectfully provide further details regarding the original complaint to assist with your assessment.

Two examples of real-world studies funded by Theramex are:

1. **Bijuva vs CEE/MPA Study (MACE Study):** This study compared Bijuva to conjugated estrogens and progestins (CEE/MPA) and focused on major adverse cardiac events (MACE).
2. **Real World Experience of the Menopause Treatment Tool (MTT):** Theramex has funded the non-interventional trial and its outputs.

We would like to highlight that, based on our observations, there appears to be little or no evidence that either of these studies has undergone the necessary procedures, as outlined in our initial letter.

Regarding prescribing information, while we did provide the PMCPA with an example, it is concerning that the lack of a centralized process means that not all products may have undergone the required reviews and updates (even when the products summary of product characteristics has undergone changes). This oversight could potentially place patients at risk, as well as leave healthcare professionals without the most up-to-date safety information."

The complainants provided the following further information in a later email:

"Additionally, it has come to light that the prescribing information for the Evorel range prescribing information was incomplete, omitting some common side effects such as uterine spasms and vaginal infection (the information was not previously updated when the product's SPCs were changed). The missing information further highlights the

ongoing issues with updating prescribing information and the communication between Global and the affiliates.

As you can appreciate, this oversight can lead to healthcare professionals (HCPs) not being fully informed of potential risks, which could jeopardize patient safety."

The complainants provided the following further information following a request from the case preparation manager:

"Regarding Intrarosa, the Global team last updated the SmPC in 2019; however, the UK team recently updated the product's prescribing information. It has been challenging to determine what exactly was missed during this process, as probing too deeply could raise suspicions. We know the PI was not thoroughly reviewed for approximately five years. Unfortunately, only the Regulatory Department holds all the correspondence from the authorities regarding the changes to the SPCs, and this information is not shared, even with our Medical colleagues at Global. There is a complete breakdown of communication between the relevant departments due to the absence of a process to update the PIs.

In relation to clinical trials, we would like to inform you that Bijura vs CEE/MPA Study (MACE Study) did not have its protocol certified, and the results were not published on third-party sites, such as stated in the Code or on the company's website as per Code. We are also aware that the Real World Experience of the Menopause Treatment Tool (MTT) faced similar issues regarding the certification and the lack of publication of results on external platforms and the company's website. Currently, there is no process to ensure the assessment and approval of clinical trials, whether interventional or non-interventional, in compliance with the Code or relevant regulations."

When writing to Theramex, the PMCPA asked it to consider the requirements of Clauses 12.1 and 5.1 in relation to the allegations regarding prescribing information for Intrarosa and the Evorel range, Clauses 4.6, 4.7, 5.1 and 8.3 in relation to the allegations regarding the Bijuva vs CEE/MPA Study (MACE Study) and the Real World Experience of the Menopause Treatment Tool and Clauses 5.1 and 2 overall of the 2021 Code.

THERAMEX'S RESPONSE

The response from Theramex is reproduced below:

"Thank you for your letter dated 16 October 2024, regarding a complaint under the 2021 Code of Practice by an anonymous Theramex employee(s).

The Complaint

The complainant(s) have expressed their concerns around the company's adherence to regulatory standards and the accountability of its leadership. They say that they have repeatedly raised concerns about the lack of processes governing the updating of prescribing information and have specifically referenced Intrarosa and Evorel in this matter. They also state that Theramex's Bijuva vs CEE/MPA study (MACE study) and Menopause Treatment Tool have not complied with the requirements relating to clinical studies.

Summary response to the complaint

Theramex takes its obligations under the ABPI Code of Practice very seriously. Accordingly, following receipt of this complaint a thorough internal investigation was conducted of the issues raised by the complainant and the matters the PMCPA has asked us to address in our response.

We will address each of the complainant's claims according to the relevant clause(s) of the ABPI Code of Practice 2021.

Prescribing Information

At the time of receipt of the complaint, Theramex did have a process in place for the Management of Regulatory Notifications. However, this process was not sufficiently robust to ensure that prescribing information (PI) was updated immediately following the relevant SPC updates as per the Code requirements.

Intrarosa PI

Since 2019, (the alleged date of last update of the Intrarosa PI by the complainant(s)), the Intrarosa PI underwent updates on the following dates:

- April 2019 – (INTRA_GB_PI_00058)
- July 2021 – (INTRA_GB_PI_004779)
- Certificate for 'INTRA_GB_PI_004779'
- Sep 2024 (INTRA_UK_EN_12708_v2(v2.0))
- Certificate for 'INTRA_UK_EN_12708_v2(v2.0)'

	2019–2020	2021–2022	2023–2024
Intrarosa			
SPC (Date of revision of the text)	Jan 2019	None available	12/10/2023
PI (Job code / Date of preparation)	INTRA_GB_PI_000582 01/04/2019	INTRA_GB_PI_004779 July 2021	INTRA_UK_EN_12708_V2 01/09/2024 Digital & Print
Date of approval for PI certificates	PI Withdrawn – not used	14/07/2021	04/09/2024 No hard copy certification

Evorel PI's

Similarly to the Intrarosa PI above, since 2019, the Evorel PI's underwent updates on the following dates:

Evorel Conti:

- June 2023 – (Evor GB_PI_010306)
- Certificate for 'Evor GB_PI_010306'
- October 2024 – (EVOR_UK_EN_20239_v1(v1.3)
- Certificate for 'EVOR_UK_EN_20239_v1(v1.3)'

	2019–2020	2021–2022	2023–2024
Evorel Conti			
SPC (Date of revision of the text)	15 June 2016 -01 Oct 2019 01 Oct 2019 Oct 2019 - Sep 2020	Track change May 2022 - June 2023	12/09/2023
PI (Job code / Date of preparation)	Not available	Evor_GB_PI_010306 June 2023	EVOR_UK_EN_20239_v1(v1.3) October 2024 Digital
Date of approval for PI certificates	Not available	12/06/2023	10/10/2024

Evorel Sequi:

- June 2023 – (Evor_GB_PI_010304)
- Certificate for 'Evor_GB_PI_010304'
- October 2024 – (EVOR_UK_EN_20240_v1(v1.3)
- Certificate for 'EVOR_UK_EN_20240_v1(v1.3)'

	2019–2020	2021–2022	2023–2024
Evorel Sequi			
SPC (Date of revision of the text)	15 June 2016 -01 Oct 2019 01 Oct 2019 Oct 2019 - Sep 2020	Track change May 2022 - June 2023	12/09/2023
PI (Job code / Date of preparation)	Not available	Evor_GB_PI_010304 June 2023	EVOR_UK_EN_20240_v1(v1.4) 10/10/24 Digital
Date of approval for PI Certificates	Not available	12/06/2023	10/10/2024

Evorel 25, 50, 75, 100:

- September 2023 – (Evor_GB_PI_011328)
- Certificate for 'Evor_GB_PI_011328'
- October 2024 – (EVOR_UK_EN_20241_v1(v1.3)
- Certificate for 'EVOR_UK_EN_20241_v1(v1.3)'

	2019–2020	2021–2022	2023–2024
Evorel 25,50,75,100			
SPC (Date of revision of the text)	01 Oct 2019 01 Oct 2019-11 Sep 2020 Track change from 11 Sep 2020 - April 2022	3 Oct 2022 - 27 June 2023 Track change from Oct 2022 - June 2023	Oct 2023
PI (Job code / Date of preparation)	Not available	Evor_GB_PI_011328 Sep 2023	EVOR_UK_EN_20241_v1 10/10/2024 Digital
Date of approval for PI certificates	Not available	15/09/2023	10/10/2024

As can be seen from the tables above, since 2019 to present, the PIs for Intrarosa and the Evorel range have undergone a thorough review and regular updates. We have however identified that, following the SPC updates, in some instances, the respective PIs were not reviewed promptly to determine whether changes were required. Following the 2023 SPC updates, we acknowledge that the PIs were updated after a year, which is unacceptable. We emphasize that immediate actions are being taken to enhance and streamline the PI management process as we recognise that the current process is not robust enough. We have a cross functional team assigned to review and update the management of PI process. We anticipate this will be updated and made effective in QI 2025.

Acknowledgement

Based on our findings, we acknowledge breaches of Clause 12.1. Given that we did not meet the standards as outlined in the Code, we admit to a breach of Clause 5.1.

Details of the studies

The PMCPA has requested details of the interventional trials which were the subjects of the complaint. Both the Bijuva MACE study and the Menopause Treatment Tool were non-interventional studies. We shall address each trial separately.

The MACE Study

The Bijuva (oral 17β-estradiol/micronized progesterone) vs. CEE/MPA (equine estrogens and medroxyprogesterone acetate) study, also referred to as the MACE (major adverse cardiac) study, compared cardiovascular risk factors between two combined oral hormonal therapies available in the United States.

This study, which comprised a retrospective analysis of insurance claims databases, was conducted in 2022 with the goal of assessing any potential differences in cardiovascular risk between Bijuva and the standard therapy, CEE/MPA. The study included data from US prescriptions and medical claims from 1.9million US practitioners. The study was funded by Theramex. We also contributed to the design of the study, the interpretation of the data, the development of the manuscript and arranging the future publication of the study. Theramex appointed a biostatistics company, [named], based in [location], to oversee the data analysis and medical writing. The retrospective analysis was approved internally. Given its nature, we did not require ethics approval.

The MACE study data was subsequently shared through the following presentations in 2024 during independent scientific sessions, and as part of promotional symposia, as detailed below:

1. [Named gynaecological endocrinology organisation] – Oral presentation by [name]
2. [Named UK menopause organisation] – Oral presentation by [name]
3. [Named menopause organisation] – Oral presentation by [name]
4. [Named gynaecological endocrinology organisation] – Presentation in a promotional symposium by [name]

5. [Named menopause organisation] – Presentation in a promotional symposium by [name]

Upon investigation, we noted the following:
- There was no study protocol.
- The results of the study were not disclosed on the Clinical Trial Registries.
- Theramex did not publish a summary of the results or the details of the study on the company website.

The Real-World Experience of the Menopause Treatment Tool (MTT)

This was a non-interventional mixed methods research validation study. The study was conducted amongst 8 HCPs per 6 countries from UK and Europe, in which a decision aid tool, the Menopause Treatment Tool (MTT) was used in consultation with women. Three women aged between the ages of 45–60 years, were identified by each of the 6 HCPs and who presented menopausal symptoms or wished to start Hormonal replacement therapy (HRT).

The Validation study and protocol was approved by the International Review Board on March 24, 2024. Regrettably, the study protocol was not certified by a Theramex authorized signatory in the manner outlined in the Code.

In addition, our investigation into this matter highlighted the following points:
- The results of the study were not disclosed on the Clinical Trial Registries.
- Theramex did not publish a summary of the results or the details of the trial on our website.

Relevant policies/SOPs

At the time of receipt of the complaint, Theramex did not have a process in place with respect to clinical studies. We are now working to put in place a robust process for all future clinical studies.

Acknowledgement

Based on our findings, we acknowledge breaches of Clause 4.7 (as these were both non-interventional studies) and 8.3. Given that we did not meet the standards as outlined in the Code, we admit to a breach of Clause 5.1.

We do not believe there has been a breach of Clause 4.6 as neither of the studies in question were clinical trials.

Details of how Theramex ensure compliance with the Code across all areas

One of the overarching aspects of the complaint is that there is a lack of accountability on the part of the leadership of the company and that concerns have been raised repeatedly but not acted on.

Compliance with the Code is hugely important to Theramex. Our Code of Conduct, which must be acknowledged by every employee, states that anyone who knows of or

suspects non-compliance must report it as soon as possible and can do so without fear of retaliation. Reporting may be anonymous if desired, via the [email address provided] email or the whistleblowing hotline. Colleagues are also encouraged to share concerns with their line manager or with trusted members of the HR, Legal or Compliance teams.

We are not aware of any of the matters in the complaint having been escalated internally (either openly or anonymously) prior to their being reported to the PMCPA but welcome the opportunity to improve our processes where they have clearly not met the standards expected by the Code and by ourselves.

Summary

We recognise that the activities listed above have fallen short of the required industry standards. The necessary steps and action plans are being put into place along with the corrective measures that have already began.

Clause 5.1

Clause 5.1 of the Code concerns the obligation to maintain high standards.

We recognise the highest standards were not met in this instance. Therefore, we accept a breach of Clause 5.1.

Clause 2

Clause 2 of the Code concerns activities or materials which might reduce confidence in the industry. Regrettably, in this case, we accept a breach of Clause 2."

FURTHER RESPONSE FROM THERAMEX

After giving preliminary consideration to the case, the Panel asked Theramex to provide copies of the summary of product characteristics issued since 1 January 2019 for each product, to supplement the tables in the response letter with the details requested by the case preparation manager regarding each update to the summary of product characteristics, and to clarify certain points in the response letter.

The response from Theramex is reproduced below:

"1. Please find enclosed, copies of each version of the summary of product characteristics issued since 1 January 2019 for:
    a. Intrarosa
    b. Evorel Conti
    c. Evorel Sequi
    d. Evorel 25
    e. Evorel 50
    f. Evorel 75
    g. Evorel 100.

Please note, with respect to Intrarosa Theramex is not the Marketing Authorisation Holder. We have attempted to get the necessary information (SPC changes); however, no updates were forthcoming.

2. Please find enclosed a table outlining the date of each SPC update and a brief description of the changes that were made. Also included is confirmation whether these changes necessitated any changes to the PI.

[The following tables were provided as a separate document]

Data from 1st Jan 2019: Intrarosa

Date of SmPC Change	A brief description of the changes	Should the changes necessitate any change in the Prescribing Information	Did the Prescribing Information Change (Y/N)
11th Mar 2019	Transfer of Marketing Authorisation	No	
1st Apr 2020	This was an application for a group of variations. A.6 – Administrative change – Change in secondary packaging site	No	
15th Sept 2022	Renewal of the marketing authorisation		
7th Dec 2023	Removal of additional monitoring requirement (black triangle no longer required)	Yes	No

Data from 1st Jan 2019: Evorel Conti

Date of SmPC Change	A brief description of the changes	Should the changes necessitate any change in the Prescribing Information	Did the Prescribing Information Change (Y/N)
Approved 21st Sept 2020	Update to align with Core HRT SmPC	Yes	No

	Update to the safety information on breast cancer risk for HRT products. (Sections 4.4 and 4.8 updated)		
Approved 12th May 2022	Update to align with Core HRT SmPC Update to safety information to add warnings on the drug-drug interaction with glecaprevir/pibrentasvir in the case of patients suffering from hepatitis C, as well as on the exacerbation of symptoms of hereditary and acquired angioedema. (Sections 4.3, 4.4, 4.5, 4.8 and 5.1)	Yes	No
Approved 12th Sept 2023	Change of registered address of Theramex HQ UK Limited. (Section 7 updated)	Yes	Yes

Data from 1st Jan 2019: Evorel Sequi

Date of SmPC Change	A brief description of the changes	Should the changes necessitate any change in the Prescribing Information	Did the Prescribing Information Change (Y/N)
Approved 18th Sept 2020	Update to align with Core HRT SmPC Update to the safety information on breast cancer risk for HRT products. (Sections 4.4 and 4.8 updated)	Yes	No
Approved 16th May 2022	Update to align with Core HRT SmPC Update to safety information to add warnings on the drug-drug interaction with glecaprevir/pibrentasvir	Yes	No

	in the case of patients suffering from hepatitis C, as well as on the exacerbation of symptoms of hereditary and acquired angioedema. (Sections 4.3, 4.4, 4.5, 4.8 and 5.1)		
Approved 12th Sept 2023	Change of registered address of Theramex HQ UK Limited. (Section 7 updated)	Yes	Yes

Data from 1st Jan 2019: Evorel 25

Date of SmPC Change	A brief description of the changes	Should the changes necessitate any change in the Prescribing Information	Did the Prescribing Information Change (Y/N)
Approved 24th Nov 2020	<u>Update to align with Core HRT SmPC</u> Update to the safety information on breast cancer risk for HRT products. (Sections 4.4 and 4.8 updated)	Yes	No
Approved 3rd Oct 2022 (sequence 0015)	<u>Update to align with Core HRT SmPC</u> Update to safety information to add warnings on the drug-drug interaction with glecaprevir/pibrentasvir in the case of patients suffering from hepatitis C, as well as on the exacerbation of symptoms of hereditary and acquired angioedema. (Sections 4.3, 4.4, 4.5, 4.8 and 5.1)	Yes	No
Approved 16th Oct 2023	Change of registered address of Theramex HQ UK Limited. (Section 7 updated)	Yes	No

Data from 1st Jan 2019: Evorel 50

Date of SmPC Change	A brief description of the changes	Should the changes necessitate any change in the Prescribing Information	Did the Prescribing Information Change (Y/N)
Approved 24th Nov 2020	Update to align with Core HRT SmPC Update to the safety information on breast cancer risk for HRT products. (Sections 4.4 and 4.8 updated)	Yes	No
Approved 3rd Oct 2022	Update to align with Core HRT SmPC Update to safety information to add warnings on the drug-drug interaction with glecaprevir/pibrentasvir in the case of patients suffering from hepatitis C, as well as on the exacerbation of symptoms of hereditary and acquired angioedema. (Sections 4.3, 4.4, 4.5, 4.8 and 5.1)	Yes	No
Approved 16th Oct 2023	Change of registered address of Theramex HQ UK Limited. (Section 7 updated)	Yes	No

Data from 1st Jan 2019: Evorel 75

Date of SmPC Change	A brief description of the changes	Should the changes necessitate any change in the Prescribing Information	Did the Prescribing Information Change (Y/N)
Approved 24th Nov 2020	Update to align with Core HRT SmPC Update to the safety information on breast	Yes	No

	cancer risk for HRT products. (Sections 4.4 and 4.8 updated)		
Approved 3rd Oct 2022	<u>Update to align with Core HRT SmPC</u> Update to safety information to add warnings on the drug-drug interaction with glecaprevir/pibrentasvir in the case of patients suffering from hepatitis C, as well as on the exacerbation of symptoms of hereditary and acquired angioedema. (Sections 4.3, 4.4, 4.5, 4.8 and 5.1)	Yes	No
Approved 16th Oct 2023	Change of registered address of Theramex HQ UK Limited. (Section 7 updated)	Yes	No

Data from 1st Jan 2019: Evorel 100

Date of SmPC Change	A brief description of the changes	Should the changes necessitate any change in the Prescribing Information	Did the Prescribing Information Change (Y/N)
Approved 21st Sept 2020	<u>Update to align with Core HRT SmPC</u> Update to the safety information on breast cancer risk for HRT products. (Sections 4.4 and 4.8 updated)	Yes	No
Approved 3rd Octo 2022	<u>Update to align with Core HRT SmPC</u> Update to safety information to add warnings on the drug-drug interaction with glecaprevir/pibrentasvir in the case of patients suffering from hepatitis	Yes	No

	C, as well as on the exacerbation of symptoms of hereditary and acquired angioedema. (Sections 4.3, 4.4, 4.5, 4.8 and 5.1)		
Approved 16th Oct 2023	Change of registered address of Theramex HQ UK Limited. (Section 7 updated)	Yes	No

3. You requested clarification on the following points that were in our response letter dated 14 November 2024,

a. "PI Withdrawn – not used" in relation to the April 2019 prescribing information for Intrarosa (INTRA_GB_PI_000582) in your response letter. What prescribing information was in use before 14 July 2021?

The following two prescribing information were used before the July 2021 version:

i. Intrarosa PI_INTRA_GB_PI_000171_Dec 2018
ii. Intrarosa Certificate_INTRA_GB_PI_000171_20 Dec 2018
iii. Intrarosa PI_INTRA_HQ_ARTCL_000031_Oct2018
iv. Intrarosa Certificate_INTRA_HQ_ARTCL_000031_20 Feb2019

b. "Not available" in relation to the prescribing information for the Evorel range prior to 12 June 2023.

The following Evorel prescribing information were used before the June 2023 version:

i. Evorel Conti PI_ THX_GB_PI_001473_Jan 2020
ii. Evorel Conti PI certification_ THX_GB_PI_001473_27 Jan 2020
iii. Evorel Conti PI_ Evor_GB_PI_006314_Jan 2022
iv. Evorel Conti PI certification_ Evor_GB_PI_006314_12 Jan 2022
v. Evorel Sequi PI_ THX_GB_PI_001474_ Jan 2020
vi. Evorel Sequi PI certification _THX_GB_PI_001474_27 Jan 2020
vii. Evorel Sequi PI_Evor_GB_PI_006313_Jan 2022
viii. Evorel Sequi PI certification_Evor_GB_PI_006313_12 Jan 2022
ix. Evorel 25,50,75,100 PI_ THX_ GB_PI_001472_Jan 2020
x. Evorel 25,50,75,100 PI certification_ THX_ GB_PI_001472_27 Jan 2020
xi. Evorel 25,50,75,100_Evor_GB_PI_006250_Dec 2021
xii. Evorel 25,50,75,100 PI certification_Evor_GB_PI_006250_06 Jan 2022"

PANEL RULING

This complaint was received from a named, contactable person who explained that they were writing on behalf of a group of concerned employees. The complaint comprised concerns about the leadership, processes and compliance culture at Theramex, with specific allegations relating to prescribing information and clinical trials/non-interventional studies.

Allegations about prescribing information (Clauses 12.1 and 5.1)

In relation to the concerns regarding the lack of updates to the prescribing information (PI), the complainants alleged that the PI for Intrarosa had not been updated since 2019 and that the PI for the Evorel range was incomplete, omitting some common side effects when the summaries of product characteristics (SPCs) were updated.

Intrarosa

The Panel reviewed the information provided by Theramex regarding the PIs and SPCs for Intrarosa. Theramex provided five PIs for Intrarosa prepared between October 2018 and September 2024:

Date of preparation	Job Code
October 2018	INTRA_HQ_ARTCL_000031
December 2018	PI_ INTRA_GB_PI_000171
April 2019	INTRA_GB_PI_00582
July 2021	INTRA_GB_PI_004779
September 2024	INTRA_UK_EN_12708_V2

Theramex submitted that it was not the Marketing Authorisation Holder (MAH) for Intrarosa and despite its efforts to obtain the necessary information regarding SPC changes, no updates were forthcoming. The Panel noted the MAH from the SPC appeared to be Endoceutics.

Theramex provided details of four SPC updates, including the transfer of the marketing authorisation in 2019, an application for a group of variations in 2020, renewal of the marketing authorisation in 2022, and the removal of the black triangle requirement in 2023. However, the Panel noted that only two SPCs were provided — one with a revision date of 12 October 2023, as opposed to December 2023 as submitted by Theramex, and the other without a revision date, but which listed 15 September 2022 as the date of the latest renewal for the marketing authorisation.

According to Theramex, only the 2023 SPC update, relating to the removal of the black triangle, required a change to the PI.

Date of SPC change submitted by Theramex	Theramex's brief description of the changes
11th Mar 2019	Transfer of Marketing Authorisation
1st Apr 2020	This was an application for a group of variations. A.6 - Administrative change - Change in secondary packaging site
15th Sept 2022	Renewal of the marketing authorisation
7th Dec 2023	Removal of additional monitoring requirement (black triangle no longer required)

The Panel was concerned by the lack of SPC documentation retained by Theramex, particularly given the critical importance of maintaining accurate and up-to-date prescribing information.

Furthermore, the Panel questioned the accuracy of Theramex's submission regarding the date of the 2023 SPC update, as the SPC listed the date of revision of the text as 12 October 2023, not December 2023.

The Panel observed that substantive updates were made to the PIs in December 2018, April 2019, and September 2024. There were no substantive updates made to the July 2021 PI.

In relation to the December 2018 PI, two notable additions were made by Theramex to the section relating to Section 4.4, Special Warnings and Precautions. The first addition, under conditions which need supervision, stated "For oestrogen products for vaginal application of which the systemic exposure to oestrogen remains within the normal postmenopausal range, it is not recommended to add a progestagen." The second addition concerned avoiding the use of condoms, diaphragms, or cervical caps made of latex due to potential damage. The Panel noted that, as it did not have SPCs prior to 2022, it was unable to determine whether these additions were in line with any SPC update; moreover, it was unclear whether any other relevant updates were required in the December 2018 PI.

Regarding the April 2019 PI, the Panel noted that this PI included the change to the marketing authorisation holder address from London to Brussels following the SPC update in March 2019. However, Theramex submitted that this PI had been withdrawn and not utilised, although no explanation was provided for this decision. The Panel disagreed with Theramex's submission that the transfer of the marketing authorisation did not necessitate a change to the PI. Clause 12.2 included, among other things, the name and address of the holder of the authorisation or the name and address of the part of the business responsible for its sale or supply. Failure to provide the required information in accordance with Clause 12.2 would be a breach of Clause 12.1.

The Panel noted the substantive updates to the 2024 PI compared to the 2021 PI included the removal of the black triangle for additional monitoring requirements and the addition of a PLGB marketing authorisation number.

The Panel noted the black triangle requirement was removed from the SPC in December 2023. However, the Panel observed that the prescribing information was not updated in this regard until September 2024.

The Panel noted the supplementary information to Clause 12 of the 2021 Code provided an exemption for the marketing authorisation number between January 2021 to January 2023. Any date beyond this point was likely to be in breach of Clause 12.2 (iv). In this regard, the Panel noted the PLGB marketing authorisation number was not added until September 2024.

The Panel also identified discrepancies and omissions when comparing the 2024 PI with the SPCs before it. For example, regarding venous thromboembolism, the PI stated that Intrarosa had not been studied in women with current or previous venous thromboembolic disease and reported one case of pulmonary embolism in the 6.5 mg group and one in the placebo group. However, the SPC provided more critical information, stating that patients should be instructed to contact their doctors immediately upon noticing potential thromboembolic symptoms, such as painful leg swelling, sudden chest pain, or dyspnoea.

Additionally, the PI omitted several points included in the SPC regarding "other conditions observed with HRT". These included the warnings that oestrogens may cause fluid retention,

necessitating careful observation of patients with cardiac or renal dysfunction, and that women with pre-existing hypertriglyceridaemia should be closely monitored during oestrogen replacement or HRT due to the risk of large increases in plasma triglycerides leading to pancreatitis. The Panel noted these warnings were present in the two SPCs before it, dated 2022 and 2023.

The Panel noted the general principle that prescribing information must be up to date and must comply with Clause 12.2 of the Code and that the prescribing information must be consistent with the SPC for the medicine. Failure to provide the required information in the prescribing information would be a breach of Clause 12.1.

Prescribing information was an important contributor to patient safety. The Panel was concerned that the prescribing information for Intrarosa had not been kept up to date in accordance with Clause 12.2. SPC updates had not been incorporated in a timely manner, including changes to the marketing authorisation details, and important information from the SPCs had been entirely omitted. The Panel considered that while key updates had eventually been included in the 2024 PI, the prescribing information still did not appear to include some requisite information from the SPCs. Failure to provide accurate and complete prescribing information was unacceptable and the Panel ruled a **breach of Clause 12.1**.

The Panel had further concerns that Theramex had not retained full copies of the relevant SPCs, which demonstrated a fundamental issue with its processes for ensuring compliance with regulatory and Code requirements. The failure to maintain records, alongside the lack of updates and continuing inconsistencies between the PI and SPCs, despite multiple Intrarosa PI updates between 2018 and 2024, was unacceptable. The Panel considered that Theramex had failed to maintain high standards and a **breach of Clause 5.1** was ruled.

Evorel range

Theramex provided copies and details of its SPCs and PIs for Evorel 25, 50, 75 and 100, Evorel Conti and Evorel Sequi.

The Panel observed that the SPCs for Evorel 25, 50, 75 and 100, Evorel Conti and Evorel Sequi had updates of the same nature which were made on the following dates:

Date of SPC Change	**Theramex's brief description of changes**
September 2020	<u>Update to align with Core HRT SmPC</u> Update to the safety information on breast cancer risk for HRT products (Sections 4.4 and 4.8 updated)
May 2022 (Evorel Conti and Sequi) October 2022 (Evorel 25, 50, 75, 100)	<u>Update to align with Core HRT SmPC</u> Update to safety information to add warnings on the drug-drug interaction with glecaprevir/pibrentasvir in the case of patients suffering from hepatitis C, as well as on the exacerbation of symptoms of hereditary and acquired angioedema (Sections 4.3, 4.4, 4.5, 4.8 and 5.1)
June 2023	Change of registered address of Theramex HQ UK Limited. (Section 7 updated)

Theramex submitted that all updates to the SPCs listed above necessitated revisions to the prescribing information (PI). Theramex provided four copies of PIs for each medicine that were drawn up between January 2020 and October 2024:

Date of PI	**Evorel Conti**	**Evorel Sequi**	**Evorel 25, 50, 75, 100**
January 2020	THX_GB_PI_001473	THX_GB_PI_001474	THX_GB_PI_001472
December 2021	–	–	Evor_GB_PI_006250
January 2022	Evor_GB_PI_006314	Evor_GB_PI_006313	–
June 2023	Evor_GB_PI_010306	Evor_GB_PI_010304	–
September 2023	–	–	Evor_GB_PI_0011328
October 2024	EVOR_UK_EN_20239	EVOR_UK_EN_20240	EVOR_UK_EN_20241_v1

The Panel determined, according to the dates of the SPC changes submitted by Theramex, that the prescribing information for each medicine appeared not to have been updated in a timely manner.

The information on the breast cancer risk for HRT products was, according to Theramex, updated in the September 2020 SPC. The Panel observed that, despite Theramex's submission that this necessitated an update to the PI, this information was not incorporated in the prescribing information until the October 2024 versions.

In relation to the 2022 SPC updates, Theramex referenced modifications to Sections 4.3, 4.4, 4.5, 4.8 and 5.1. Specifically, it described the following additions:

Section 4.4 – Other Conditions:
- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

Section 4.4 – ALT Elevations:
- During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen glecaprevir/pibrentasvir. See section 4.5

Section 4.5 – Pharmacodynamic Interactions:
- During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women

using ethinylestradiol-containing medicinal products such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (see section 4.4).

The Panel observed that the 2022 SPC updates in relation to ALT elevations and pharmacodynamic interactions were entirely omitted from the subsequent 2023 and 2024 PIs, despite Theramex's submission that these updates necessitated a change in the PI.

The Panel noted that while Clause 12.2 did not explicitly require the inclusion of drug–drug interactions in the PI, the existing PIs did contain some information on interactions with other medications. It was therefore important that the information provided was comprehensive, accurate, and up to date in this regard.

With regard to the SPC update in June 2023 concerning the change of Theramex's registered address from Sloane Square House to 50 Broadway, the Panel noted Clause 12.2 required, among other things, the name and address of the holder of the authorisation or the name and address of the part of the business responsible for its sale or supply be included in the PI. The PIs for Evorel Conti and Evorel Sequi were promptly updated to reflect this change, whereas the PI for Evorel patches (25, 50, 75, 100 mg) was updated three months later in September 2023.

The Panel further observed that several substantive changes had been made to the 2024 PIs for each medicine which did not form part of Theramex's submission.

The Panel noted the general principle that prescribing information must be up to date and comply with Clause 12.2 of the Code which included, among other things, a succinct statement of common adverse reactions likely to be encountered in clinical practice, serious adverse reactions and precautions and contraindications. The prescribing information must be consistent with the SPC for the medicine.

The Panel considered that failure to provide the required information in the prescribing information would be a breach of Clause 12.1.

While the Panel was not an investigatory body and a detailed examination of every update across all versions of each medicine's SPC and PI was not feasible, it considered that it nonetheless had a responsibility to assess the gravity of the matter. Accordingly, the Panel limited its review to the following sections of the product SPCs:

1. Section 4.3 (Contraindications), given its critical importance to patient safety.
2. Section 4.4 (Special Warnings and Precautions), as this was highlighted by Theramex as having been updated for the Evorel range
3. Section 4.8, Undesirable effects: Adverse Drug Reactions, cited by the complainant

The Panel's observations relating to these sections, and whether they were reflected in the various PIs, are set out in detail below under separate subheadings for each medicine.

Evorel 25, 50, 75 and 100

The Panel reviewed the PIs for Evorel 25, 50, 75 and 100 and noted the 2021 PI included the addition of “flatulence” and “breast enlargement” as uncommon side effects when compared to the 2020 PI.

The Panel further observed the following substantive changes to the 2024 PI:

Contraindications (Section 4.3):

- Addition of “untreated endometrial hyperplasia”
- Change from “previous idiopathic or current VTE” to “previous or current VTE”
- Removal of “pre-malignant” tumours from contraindications

Special Warnings and Precautions (Section 4.4):

- Addition of “For the treatment of menopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life”
- Addition that “physical (including pelvic and breast) examination should be guided by this and by the contra-indications and warnings for use”
- Updated reference to diabetes mellitus to include “with or without vascular involvement” under “Conditions which need supervision”
- Addition of “Special warnings and precautions for use are also required in respect to: Endometrial hyperplasia and carcinoma, Breast cancer, Ovarian cancer, Venous thrombo-embolism, Coronary Artery disease, Ischaemic stroke, Hypothyroidism, Angi-oedema – please refer to the SmPC for full details”*

  *The Panel queried whether mere reference to the special warnings and precautions was sufficient. For example, referring readers to the SPC for venous thromboembolism did not make clear the critical action in the SPC that therapy should be discontinued if venous thromboembolism develops and that patients should be instructed to contact their doctors immediately upon noticing potential thromboembolic symptoms, such as painful leg swelling, sudden chest pain, or dyspnoea.

Adverse Drug Reactions (Section 4.8, Undesirable effects):

- “Weight increase” changed to “weight change” as a common side effect*
- “Oedema peripheral” changed to “Generalised oedema” as an uncommon side effect

  *In relation to the first point, the Panel noted that all SPCs provided by Theramex listed both weight increase and weight decrease as common side effects. However, the first two PIs for Evorel 25, 50, 75 and 100 included “weight increase” as a common adverse event; there was no reference to “weight decrease”. The Panel noted the 2024 PI had been updated to “weight change”, reflecting a more accurate and complete description of the side effects in this regard.

Other Changes:

- Updates to patch use guidance and missed dose information
- Addition of “Overdose: Effects can if necessary be reversed by removal of the patch”

The Panel did not have information before it regarding when these changes were introduced to the Evorel SPC but observed that all of these updates were already present in the earliest SPC provided by Theramex, which was revised in September 2020.

Evorel Conti

The Panel reviewed the PIs for Evorel Conti and noted the following substantive changes to the 2024 PI. The Panel did not have information before it regarding when these additions were introduced to the Evorel Conti SPC but observed that all of these updates were included in the earliest SPC provided by Theramex, which was revised in September 2020.

Adverse Drug Reactions (Section 4.8, Undesirable effects):

- Added “breast tenderness” as a very common adverse event.
- Added “affect lability”, “dyspepsia”, “acne”, “dry skin”, “pain in extremity”, “uterine spasms” and “vaginal infection” as common adverse events.
- Added “migraine” and “transaminases increase” as uncommon adverse events.
- Added “gallbladder disorder, myasthenia, uterine leiomyoma, and fallopian tube cysts” as rare adverse events.
- Added “cholestatic jaundice” as a very rare adverse event.

Special Warnings and Precautions (Section 4.4):

- Addition of “For the treatment of menopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life with careful appraisal of the risks and benefits at least annually. Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited.”
- Addition of “and together with contra-indications and warnings for use, should guide physical (including pelvic and breast) examination.” (in relation to taking a complete medical history.
- Updated reference to diabetes mellitus to include “with or without vascular involvement” under “Conditions which need supervision”
- Addition of “Special warnings and precautions for use are also required in respect to: Endometrial hyperplasia and carcinoma, Breast cancer, Ovarian cancer, Venous thrombo-embolism, Coronary Artery disease, Ischaemic stroke, Hypothyroidism, Angioedema – please refer to the SmPC for full details”*

  *The Panel queried whether mere reference to the special warnings and precautions was sufficient. For example, referring readers to the SPC for venous thromboembolism did not make clear the critical action in the SPC that therapy should be discontinued if venous thromboembolism develops and that patients should be instructed to contact their doctors immediately upon noticing potential thromboembolic symptoms, such as painful leg swelling, sudden chest pain, or dyspnoea. Similarly, the PI did not include monitoring thyroid function for patients who required thyroid hormone replacement therapy while on HRT.

Contraindications (Section 4.3):

- Addition of “untreated endometrial hyperplasia”.

Other Changes:

- Updates to patch use guidance and missed dose information.

Evorel Sequi

The Panel reviewed the PIs for Evorel Sequi and noted the following substantive changes to the 2024 PI.

Contraindications (Section 4.3):

- Addition of “untreated endometrial hyperplasia”.

Special Warnings and Precautions (Section 4.4):

- Addition of “For the treatment of menopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life with careful appraisal of the risks and benefits at least annually. Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited”
- Addition of “and together with contra-indications and warnings for use, should guide physical (including pelvic and breast) examination.” (in relation to taking a complete medical history.
- Addition of “Special warnings and precautions for use are also required in respect to: Endometrial hyperplasia and carcinoma, Breast cancer, Ovarian cancer, Venous thrombo-embolism, Coronary Artery disease, Ischaemic stroke, Hypothyroidism, Angioedema – please refer to the SmPC for full details”*

  *The Panel queried whether mere reference to the special warnings and precautions was sufficient. For example, referring readers to the SPC for venous thromboembolism did not make clear the critical action in the SPC that therapy should be discontinued if venous thromboembolism develops and that patients should be instructed to contact their doctors immediately upon noticing potential thromboembolic symptoms, such as painful leg swelling, sudden chest pain, or dyspnoea. Similarly, the PI did not include monitoring thyroid function for patients who required thyroid hormone replacement therapy while on HRT.

Adverse Drug Reactions (Section 4.8, Undesirable effects):

- Added “breast tenderness” as a very common adverse event.
- Added “dyspepsia”, “acne”, “dry skin”, “pain in extremity”, “genital discharge”, “uterine spasms” and “vaginal infection” as common adverse events.
- Added “generalised oedema” and “transaminases increase” as uncommon adverse events, and changed “breast cancer” to “breast neoplasms”.
- Added “gallbladder disorder”, “myasthenia”, “uterine leiomyoma” and “fallopian tube cysts” as rare adverse events.
- Added “gallbladder disorder” and “myasthenia” as rare adverse events.
- Added “cholestatic jaundice” as a very rare adverse event.

  The Panel observed that unlike the PI for Evorel Conti, Evorel Sequi’s PI did not list “uterine leiomyoma” and “fallopian tube cysts” as rare adverse events, nor did it include “with or without vascular involvement” for diabetes mellitus under “Conditions which need supervision”. This information was present in the 2020 Evorel Sequi SPC.

Other Changes:

- Updates to patch use guidance and missed dose information.

The Panel did not have information before it regarding when all of these additions were introduced to the Evorel Sequi SPC but noted that, except for one change, all additions were included in the earliest SPC provided by Theramex, which was revised in September 2020. The exception was the update of the uncommon adverse event from “breast cancer” to “breast neoplasms” in the 2022 SPC, which was reflected in the 2024 PI.

Rulings relating to the Evorel range prescribing information

Prescribing information was an important contributor to patient safety. The Panel was concerned that numerous SPC updates had not been incorporated in a timely manner and important information from the SPCs regarding adverse events, contraindications, special warnings and precautions had been omitted since as early as September 2020. The Panel considered that while key updates had eventually been included in the 2024 PI, the prescribing information still did not appear to include some requisite information. Failure to provide accurate and complete prescribing information was unacceptable and the Panel ruled **three breaches of Clause 12.1** in relation to the Evorel range (Evorel 25,50,75 and 100, Evorel Conti and Evorel Sequi).

The Panel was further concerned with the quality of Theramex’s response; the Panel had made a number of findings that did not form part of Theramex’s submission and aspects of Theramex’s response were inaccurate. The Panel considered the company’s failure to incorporate updates and ensure the PI met the requirements of Clause 12.2 demonstrated a fundamental issue with its processes for ensuring compliance with regulatory and Code requirements. The Panel considered that Theramex had failed to maintain high standards and a **breach of Clause 5.1** was ruled.

Allegations about clinical trials/non-interventional studies (Clauses 4.6, 4.7, 8.3 and 5.1)

The complainants alleged that numerous trials, particularly real-world evidence studies presented at international congresses, did not meet the requirements of the Code.

The complainants cited two particular studies. For each study, the complainants alleged that:

- the study protocol was not certified,
- the results were not published on third-party sites, and
- neither a summary of the results nor the details of the study were published on the company’s website.

Clause 8.3 required that protocols relating to non-interventional studies must be certified in advance in a manner similar to that provided for by Clause 8.1.

Clause 4.6 required that companies must disclose details of clinical trials and include on the homepage of their website information as to where details of their clinical trials can be found.

Clause 4.7 required that companies must publish the summary details and results of non-interventional studies of marketed medicines in a manner consistent with their parallel obligations with respect to clinical trials.

The MACE study

The first study at issue was titled 'Major Adverse Cardiovascular Event (MACE) Risk in Menopausal Women Treated With Oral Estradiol/Micronised Progesterone Versus Conjugated Estrogens/Medroxyprogesterone: A Claims Data Analysis in the United States'. Theramex submitted that it was a non-interventional study that compared cardiovascular risk factors between two combined oral hormonal therapies available in the United States. The study was funded by Theramex, who also contributed to the design of the study, the interpretation of the data, the development of the manuscript, and arranging the future publication of the study. In this regard, the Panel noted four of the authors were from the UK, two of whom were UK-based Theramex employees.

The Panel noted Theramex's submission that there was no study protocol for the MACE study. As no study protocol had been certified, the Panel ruled a **breach of Clause 8.3**, as acknowledged by Theramex.

Clause 4.6 included that companies must disclose details of clinical trials and include on the home page of their website information as to where details of their clinical trials can be found. Clause 4.7 required that companies must publish the summary details and results of non-interventional studies of marketed medicines in a manner consistent with their parallel obligations with respect to clinical trials.

The Panel was concerned by Theramex's submission that the results of the MACE study were not disclosed on the Clinical Trial Registries and that neither a summary of the results nor details of the study were published on the company's website in a manner consistent with Clause 4.6. The Panel therefore ruled a **breach of Clause 4.7**, as acknowledged by Theramex.

As the MACE study was a non-interventional study, and Clause 4.6 related specifically to clinical trials, the Panel ruled **no breach of Clause 4.6**.

The Real-World Experience of the Menopause Treatment Tool (MTT)

The second study at issue was a non-interventional mixed methods research validation study for the Menopause Treatment Tool (MTT), a decision aid tool used in consultation with women from the UK and Europe.

The Panel noted Theramex's submission that the validation study and protocol was approved by the International Review Board but that the study protocol had not been certified by a Theramex authorised signatory in the manner outlined in the Code. The Panel therefore ruled a **breach of Clause 8.3**, as acknowledged by Theramex.

The Panel was concerned by Theramex's submission that the results of the MTT study were not disclosed on the Clinical Trial Registries and that neither a summary of the results nor details of the study were published on the company's website in a manner consistent with Clause 4.6. The Panel therefore ruled a **breach of Clause 4.7**, as acknowledged by Theramex.

As the MTT study was a non-interventional study, and Clause 4.6 related specifically to clinical trials, the Panel ruled **no breach of Clause 4.6**.

Maintenance of high standards in relation to non-interventional studies

The Panel noted Theramex's submission that "at the time of receipt of the complaint, Theramex did not have a process in place with respect to clinical studies. [Theramex was] now working to put in place a robust process for all future clinical studies." It was not clear to the Panel whether this statement was in direct response to the complainants' general allegation that "currently, there is no process to ensure the assessment and approval of clinical trials, whether interventional or non-interventional, in compliance with the Code or relevant regulations" or whether it was related more specifically to the requirements of Clauses 4.7 and 8.3. Regardless, the Panel considered that it was important for companies to have policies and standard operating procedures to communicate corporate standards, expectations and behaviour.

The Panel considered that transparency was a key principle for self-regulation and important for ensuring public trust in the industry. The Panel was concerned by the lack of transparency demonstrated by Theramex in not disclosing the details of the two studies in the appropriate manner and also by the apparent absence of appropriate procedures around the production and certification of the study protocols. The Panel concluded that Theramex had failed to maintain high standards in this regard and ruled a **breach of Clause 5.1**, as acknowledged by Theramex.

Allegations about leadership, culture and processes (Clause 5.1)

The complainants made a number of allegations that the Panel considered were broadly related to Theramex's leadership, culture and processes regarding Code compliance:

- that they were particularly troubled by the lack of clear leadership from the executive leadership team,
- that the complainants had attempted to escalate these issues internally on numerous occasions but there had been a consistent lack of action or meaningful response,
- that there had been no substantive action, despite the complainants having repeatedly raised concerns about the lack of processes governing the updating of prescribing information,
- that information about complaints received was not communicated to enable lessons to be learned and corrective measures implemented,
- that there was a lack of resources within Theramex's global headquarters to ensure compliance,
- that, should compliance issues arise, the signatory responsible for certifying the material should be blamed, and
- that the results of an internal audit on the approval/certification process for promotional and non-promotional material had not been shared and would show there was a "complete lack of understanding of the Code".

While noting the important nature of the allegations, the Panel considered that the complainants had provided no additional evidence in support of them. The Panel noted the difficulty in dealing with complaints based on one party's word against the other; it was often impossible in such circumstances to determine precisely what had happened. All complaints were judged on the evidence provided by the parties and the complainant had the burden of proving their complaint on the balance of probabilities. The Panel was, however, concerned that the group of employees had felt strongly enough to raise their concerns about the company with an external body.

The Panel noted Theramex's submission that it was not aware of any of the matters in the complaint having been escalated internally (either openly or anonymously) prior to their being reported to the PMCPA. Theramex submitted that its code of conduct stated that anyone who knows of or suspects non-compliance must report it as soon as possible and can do so without fear of retaliation. Reporting may be anonymous if desired, via an email address or whistleblowing hotline. The Panel was not provided with a copy of the code of conduct.

The Panel noted Theramex's acknowledgement that its activities detailed in this case had "fallen short of the required industry standards" and that it would "welcome the opportunity to improve [its] processes where they have clearly not met the standards expected by the Code and by [itself]".

The Panel noted the complainant's allegation regarding concerns about the lack of processes governing the updating of prescribing information and that there was "a complete breakdown of communication between the relevant departments due to the absence of a process to update the PIs".

The Panel had been provided with only one of Theramex's standard operating procedures (SOPs), titled 'Management of Regulatory Notifications'. The Panel was concerned that the SOP was notably brief and lacked essential details. In particular, it did not include any timelines or deadlines, nor was any sense of urgency reflected in the SOP. While the earliest issues in the complaint dated back to 2020, the Panel noted that the SOP before it had been issued relatively recently, in 2022. The Panel had not been provided with any information about what, if any, procedures were in place prior to this. In any instance, it was clear to the Panel that even with the SOP in place, Theramex had still failed to promptly update prescribing information.

The Panel considered the lack of detail in the SOP undermined its effectiveness and reflected inadequate governance of a critical process. Good governance of the process for communicating changes to the SPC was critical and had potential patient safety implications. Some SPC updates might require an update to prescribing information and the subsequent withdrawal of existing promotional material.

The Panel considered that the quality of the 'Management of Regulatory Notifications' SOP and Theramex's acknowledgement that, at the time of the complaint, it had no process in place with respect to clinical studies raised concerns about Theramex's compliance processes. The Panel considered that Theramex had failed to maintain high standards and ruled a **breach of Clause 5.1**, as acknowledged by Theramex.

Overall (Clause 2)

The Panel considered that self-regulation relied on transparency, among other things, and noted that transparency was one of the four ABPI principles. The Panel was concerned by Theramex's submission that, at the time of the complaint, it did not have a process in place with respect to clinical studies, and by the lack of transparency demonstrated in not disclosing details of the two studies in the appropriate manner.

The Panel was extremely concerned about Theramex's failures to promptly update prescribing information following changes to the SPC and the quality of the relevant SOP. Key safety information regarding adverse events, contraindications, special warnings and precautions had not been included in prescribing information and Theramex had failed to provide up-to-date

prescribing information for some products for several years. The Panel considered that it was crucial that health professionals and others could rely upon the industry for up-to-date and accurate information about their medicines – particularly new information, the omission of which could potentially impact patient safety.

Clause 2 was a sign of particular censure and reserved for such use. The Panel considered that the cumulative effect of Theramex's failings in this case was such as to bring discredit upon or reduce confidence in the pharmaceutical industry. The Panel ruled a **breach of Clause 2**, as acknowledged by Theramex.

The Panel noted that compliant and robust processes, which were appropriately trained into an organisation, were the basics of any compliance programme. In this case, the failings reflected either a complete lack of awareness of the requirements of the Code or a profound misunderstanding of its application. For such serious breaches to have occurred, and for them to have gone undetected and unremedied over a prolonged period, was wholly unacceptable and indicated a systemic failure in compliance oversight.

The Panel also had concerns about the quality of Theramex's response to this complaint. The Panel considered that Theramex should have had easy access to information about exactly what had changed in each update of the SPC and PI and be able to provide this information to the Panel in a clear manner. The Panel noted that, in the first letter to the company, the case preparation manager requested "a table showing the dates of SPC updates, brief description of the nature of changes and whether this necessitated any change to the prescribing information". The Panel was concerned that despite a follow-up request, Theramex's response lacked clarity and completeness.

In light of the cumulative nature and seriousness of breaches of the Code ruled in this case, along with the concerns about the quality of Theramex's response to this complaint, the Panel decided to **report the company to the Code of Practice Appeal Board**, in accordance with Paragraph 10.2 of the Constitution and Procedure for the Appeal Board to consider in relation to Paragraph 13.4.

COMMENTS FROM THERAMEX ON THE REPORT

Theramex's written response is reproduced below:

> "You will have seen that we have signed the form of undertaking and assurance and accept the Panel's rulings. At the same time, we did want to share with you some of the improvements which have been implemented within our organisation in relation to these matters, and we would be grateful if you could pass these details on to the Appeal Board. We have also made comments about the final case report in advance of us receiving the proposed final text in the coming weeks.
>
> As you might expect, we did not wait for the outcome of the recent code case and have already been addressing the points we raised in our submission to the Panel. This has led to the introduction of additional training sessions and the development of new ways of working and new procedural documents.
>
> We also wanted to communicate that we are working with an highly regarded external provider of compliance services in the UK who will perform over the next few weeks a

detailed and objective assessment of our compliance program and help identify any further improvements which are required.

Prescribing Information

The Panel noted that the SOP entitled 'Management of Regulatory Notifications' was too brief and lacked essential details regarding the prescribing information update process. We have already addressed this point and it has been remedied by the introduction of a new SOP – Creation and maintenance of Prescribing Information, which became effective late last year on 23 December 2024. This sets out a detailed framework for this process and includes clear timelines and responsibilities.

We have also noted the Panel's request that Theramex undertake a thorough review of all PIs. Again, this work was implemented and completed some time ago.

We thank the Panel for the specific comments in the case report and are currently considering them.

However, we are conscious that the Panel has drawn attention to specific points that were not raised by the complainants. We recognise that to reach an overall position on rulings, the Panel might debate matters beyond the specifics raised by complainants, but the remit of the Panel specifically restricts it from being an investigatory body. There are also very definite self-regulatory and legal implications should it be perceived that the PMCPA is directing the content of official safety instructions from any manufacturer or publicly proactively drawing attention to what it perceives as weaknesses in said documentation (such as Prescribing Information) in the absence of specific allegations on those detailed points. In that regard we do not feel it is appropriate for any of the Panel's detailed interrogation of the SPC and PI to be made public in the final case report, beyond those that directly address the specific elements raised by the complainants.

Clinical trials/non-interventional studies

We acknowledge the Panel's ruling that Theramex was in breach of Clause 4.7 and have now created a dedicated area of the corporate website which will contain the details of all prospective and retrospective non-interventional studies, and which already includes the two retrospective non- interventional studies which were the subject of the complaint."

APPEAL BOARD'S CONSIDERATION OF THE REPORT FROM THE PANEL

The Appeal Board took account of the Panel's comments and rulings of breaches of the Code, including Clause 2, and its decision to report Theramex to the Appeal Board.

The Appeal Board heard from the representatives from Theramex at the Appeal Board meeting that the company fully acknowledged and accepted accountability for the compliance failings that were identified. The representatives confirmed that these failures reflected deeper deficiencies in internal processes and governance structures, specifically around the timely updating of information. The representatives presented details of Theramex's preventative actions, changes, training and process improvement.

During questioning, the representatives from Theramex welcomed the suggestion to undertake a staff survey. This would be especially relevant given that this case had arisen from a complaint from some of its employees.

The Appeal Board recognised that Theramex was a small company that had changed in function and was rapidly growing and this posed challenges.

The Appeal Board noted that an external compliance audit was currently underway within the company. The Appeal Board welcomed the company's initiation of an external compliance audit and felt that the company's representatives at the meeting had expressed a sincere desire to improve. The Appeal Board was, however, very concerned about the fundamental compliance errors highlighted by this case, particularly those relating to safety and regulatory issues that were fundamental to protecting patients. The Appeal Board considered that it was essential that the company make substantial progress to ensure such issues did not recur. The Appeal Board strongly encouraged Theramex to ensure that the external compliance audit was broad enough to focus on matters affecting patient safety as a priority.

The Appeal Board decided, in accordance with Paragraph 13.4 of the 2024 Constitution and Procedure, that a senior representative of Theramex should be invited to attend the Appeal Board meeting on 10 December 2025 to report on progress, and confirm that appropriate action had been taken. The Appeal Board requested this include a presentation on the scope and outputs from the external compliance audit and any staff survey results, together with a detailed compliance action plan to address any issues identified, including dates and timescales. The Appeal Board reserved the decision regarding the application of additional sanctions until consideration of this information at the December 2025 Appeal Board meeting.

CASE UPDATE

By agreement, consideration of this case was postponed from the December 2025 Appeal Board meeting to the February 2026 meeting.

On 28 January 2026, however, Theramex informed the PMCPA that it would no longer accept the jurisdiction of the PMCPA or be part of the self-regulatory framework for the pharmaceutical industry in the UK.

Theramex declined to attend the February 2026 Appeal Board meeting or provide any written submission in relation to the Appeal Board's request outlined above.

APPEAL BOARD CONSIDERATION

The Appeal Board considered that withdrawing from self-regulation whilst under consideration of further sanctions by the Appeal Board in relation to fundamental compliance errors, particularly those relating to safety and regulatory issues that were fundamental to protecting patients, was extremely disappointing and evidenced a failure to take responsibility for these failures within the self-regulatory framework.

Further, the Appeal Board was extremely disappointed that Theramex has, in the Appeal Board's view, by withdrawing from self-regulation, shown a derogation of responsibility under self-regulation as a pharmaceutical company to its employees and, most importantly, to public

safety. By the company's failure to provide the Appeal Board with evidence of the actions taken since May 2025 to address the significant issues identified and requiring the MHRA to assume full responsibility for regulating the company, Theramex has inevitably delayed any regulatory action and oversight.

The Appeal Board had no evidence before it to show that Theramex had taken any action to improve since May 2025. Taking everything into account, in accordance with Paragraph 13.4 of the Constitution and Procedure, the Appeal Board decided that Theramex should be publicly reprimanded and, in addition, that the company should be audited by the PMCPA. The wording of the public reprimand is given below.

> "Theramex HQ UK Ltd has been publicly reprimanded by the Code of Practice Appeal Board for the fundamental compliance errors highlighted by this case, including failing to provide up-to-date prescribing information leading to breaches of the ABPI Code. Further, the Appeal Board considered Theramex's decision to leave self-regulation while sanctions were ongoing and the case was not yet complete, evidenced a failure to take responsibility for addressing its failings within the self-regulatory framework.
>
> In Case/0303/09/24, the Code of Practice Panel ruled 13 breaches, including that Theramex had brought discredit upon, and reduced confidence in, the pharmaceutical industry. The Panel was particularly concerned about Theramex's failures to promptly update prescribing information following changes to the summary of product characteristics and thereby failing to provide up-to-date prescribing information for the Evorel (estradiol) range and Intrarosa (prasterone) for several years. The Panel, concerned that the breaches indicated a systemic failure in compliance oversight, reported the company to the Appeal Board, in accordance with Paragraph 10.2 of the Constitution and Procedure.
>
> At the May 2025 Appeal Board meeting, representatives of Theramex fully acknowledged the failures "reflected deeper deficiencies in internal processes and governance structures specifically around the timely updating of information and ensuring appropriate transparency" but assured the Appeal Board that Theramex had taken steps to address these specific issues and the company was improving both process and training and Theramex had commissioned a third-party external compliance audit. The Appeal Board was very concerned about the "fundamental compliance errors… particularly those relating to safety and regulatory issues that were fundamental to protecting patients" and required that a senior representative of Theramex be invited to attend the December 2025 meeting to report on the outputs from the external compliance audit and any staff survey results, and present a detailed compliance action plan to address any issues identified. The Appeal Board reserved the decision regarding the application of additional sanctions until consideration of this information. This meeting was subsequently postponed, by agreement, until February 2026.
>
> On 28 January 2026, ahead of the February 2026 Appeal Board meeting, Theramex informed the PMCPA that it would no longer accept the jurisdiction of the PMCPA or be part of the self-regulatory framework for the pharmaceutical industry in the UK. Theramex declined to attend the February 2026 Appeal Board meeting or provide a written submission in relation to the Appeal Board's request outlined above.

The Appeal Board is extremely disappointed that Theramex has decided to leave self-regulation having been found in breach of the Code, but while sanctions were ongoing and the case was not yet complete. It is the Appeal Board's view that this shows a derogation of responsibility under self-regulation as a pharmaceutical company to its employees and, most importantly, to public safety. By the company's failure to provide the Appeal Board with evidence of the actions taken since May 2025 to address the significant issues identified and requiring the MHRA to assume full responsibility for regulating the company, Theramex has inevitably delayed any regulatory action and oversight.

In addition to the public reprimand, the Appeal Board also decided to require an audit of Theramex's procedures in relation to the Code to be carried out by the PMCPA. Theramex must comply with the requirement for a PMCPA audit should it request to rejoin self-regulation in the future.

The PMCPA is no longer responsible for Theramex under the self-regulatory framework and the company is now fully under the responsibility of the Medicines and Healthcare products Regulatory Agency."

Complaint received	**30 September 2024**
Undertaking received	**16 April 2025**
Appeal Board consideration	**22 May 2025 and 26 February 2026**
Interim case report first published	**21 July 2025**
Theramex withdrew its agreement to accept the jurisdiction of the PMCPA	**28 January 2026**
Case completed	**26 February 2026**